REMARKS

Applicants have amended the claims in order to more particularly define the invention taking into consideration the outstanding Official Action and the elected invention. All of the claims have been canceled from the application without prejudice or disclaimer and reserving Applicants' right to file a divisional application directed to the non-elected subject matter.

More particularly, claims 40-48 have been added to the application to the elected invention and relate to claims 1 and 5-12 which have been considered on the merits. Applicants most respectfully submit that all the claims now present in the application are in full compliance with 35 U.S.C. 112 and are clearly patentable over the references of record.

Applicants wish to emphasize that original claim 1 of the PCT application stated that the vaccine comprises a defined amount of "at least three different types of colonization factor antigens". This limitation has now been inserted into the claims which specify at least 100 μg of at least three different types of colonization factor antigens, from the original claim 2 or from the latest claim 8. This is set forth in new claim 40.

Furthermore, Applicants have noted the Examiner's objection to the phrase "which vaccine composition does not contain heat stable enterotoxin (ST)" at the end of claim 1. This has been deleted and the language "wherein heat stable enterotoxic (ST) of said E. coli is removed from said antigens if present" added in accordance with the amendment by the Examiner in connection with the Notice of Allowability and Notice of Allowance and Issue Fee dated mailed February 5, 2003. Thus, this limitation is clearly supported by Applicants' specification as originally filed and as would be appreciated by one of ordinary skill in the art to which the invention pertains.

In addition, the amended claims take into consideration the objections to the claims pointed out by the Examiner in the Official Action and therefore, it is most respectfully requested that the rejections of claims 1 and 5-12 under 35 U.S.C. 112, first and second paragraphs, be withdrawn in view of the amendments to the claims.

The rejection of claims 1 and 5-12 under 35 U.S.C. 102(b) as being anticipated by Savarino et al. has been carefully considered. In this regard, it is noted that the Examiner has cited the Holmgren et al. reference is not used as a secondary reference in combination with Savarino et al. but rather is used to show that every element of the claimed subject matter is disclosed by Savarino with the unrecited limitations being inherent in view of the known art as explained above. This rejection has been carefully considered but is most respectfully traversed in view of the amendments to the claims and the following comments.

With respect to the anticipation rejection, Applicants wish to direct the Examiner's attention to MPEP § 2131 which states that to anticipate a claim, the reference must teach every element of the claim.

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed.Cir. 1990).

Where in the reference is all of the limitations now set forth in the claims now present in the application? Accordingly, it is most respectfully requested that the anticipation rejection be withdrawn in view of the further amendments to the claims.

The Official Action states on page 5, lines 6-7, that the prior art ETEC SBL strains are structurally the same as the ones recited in the instant claims, they are expected to produce or contain the same amount of the various CFA on CS-antigens. However, this is not the case and this statement is specifically traversed.

Applicants wish to point out that for the success of the vaccine composition of the invention it is necessary to have at least three different types of colonization factor

antigens, each present in an amount of at least 100 µg, and therefore this statement of amounts is now inserted into new claim 40, the new main claim corresponding to claim 1.

The Examiner assumes that the vaccine composition of the present invention is the same as Savarino et al. vaccine, but the Savarino et al. reference only states the types of colonization factor antigens and the number of killed *E. coli*. There is no control of the amount of the different colonization factor antigens present.

As already stated in the present PCT application on pag 2, lines 8-9: "For product safety and efficiency a vaccine composition must be non-infectious and contain defined amounts of active ingredients which are the same from batch to batch".

For a vaccine composition it is thus necessary to have a defined amount, or at least a defined lower amount, of antigens that trigger the immune response of the vaccinated patient.

However, there are problems in the cultivation of *E. coli* to obtain commercial quantities of the ETEC bacteria with CFAs and their sub-components (CS-antigens).

As mentioned in the present PCT application on page 2, the first lines, there were problems with the scaling up of the production of ETEC bacteria having CFAs, and a solution to the problems were disclosed in the applicants International Patent Application WO 95/33825 (issued as U.S. Patent No. 5,935,838).

Applicants cite from the WO 95/33825:

"In WO 92/14487 a method for production and use of an oral ETEC vaccine is disclosed. The ETEC bacteria are grown at 37 degrees Centigrade from agar plates to liquid medium in order to obtain commercial quantities of the ETEC bacteria with CFAs and their subcomponents (CS-antigens). These subsequently formalin killed bacteria may then be used as an oral vaccine against the ETEC bacteria. The CFA and CS antigens will thus function as antigens in the immunological processing that will take place in the intestine.

In the scaling up of the production of ETEC bacteria having CFAs it was surprisingly found that the bacteria lost their ability to produce CFAs more and more for

each new generation. In the studying of the reason for this, it was noticed that the loss of the ability of the bacteria to produce CFAs at temperatures above room temperature was accompanied by a loss f the regulatory gene localized in a plasmid in the bacteria."

The WO 92/14487 is the Holmgren et al. reference cited by the Examiner as U.S. 6,558,678.

In the Savarino et al. reference is stated under Materials and Methods that the ETEC/rCTB vaccine (E003) was produced by SBL Vaccin (Stockholm). Applicants now enclose an Analysis Certificate, Reanalysis of the Lot no: E 003A.

From the summary protocol it is evident that the date of manufacture of the lot E 003A was June 21, 1994. The fimbrial antigen content in an ELISA test (Mab) show that there were >20 µg/dose of each of CFA/I, CS1, CS2, CS4 and CS5. As just explained, SBL had trouble to produce higher amounts of the fimbrial antigen on *E. coli* at that time, and therefore cut-off was set at 20 µg.

In the present invention the vaccine should contain at least 100 µg of each colonization factor antigen present in the vaccine composition. Accordingly, it is most respectfully requested that this rejection be withdrawn.

In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,

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